"XP-002099834", (hereinafter referred to as "Hasegawa"), in view of European Patent Application No. EP 0594612 of Miettinen, *et al.* ("Miettinen") and U.S. Pat. No. 5,277,910 of Hidvégi ("Hidvégi"), for the reasons of record set forth in the Office Action dated August 29, 2001 (Paper No. 12). In Paper No. 16, the Examiner makes the rejection final.

The Examiner insists that the use of a conjugated fatty acid, as claimed, is suggested by the prior art, and that one of ordinary skill in the art would have reasonably expected the combination of a phytosterol and a conjugated fatty acid to result in an improved therapeutic effect. (See, Paper No. 16, p. 3). Additionally, the Examiner contends that Applicant's rebuttal of the alleged *prima facie* case of obviousness, supported by evidence showing significantly improved results as compared to the prior art, is not persuasive.

Applicant strenuously, but respectfully, traverses the Examiner's rejections, the contentions and arguments in support thereof, and the dismissal of the indicia of non-obviousness, as set forth in Paper No. 16, for the reasons set forth below.

To summarize:

❶ A prior art recitation of fatty acids, including unsaturated fatty acids, in combination with a phytosterol, does not equate to a teaching or a suggestion to combine a phytosterol and a *conjugated* fatty acid.

❷ None of the four references teaches or suggests a hypocholesteremic preparation comprising; (i) a phytostenol or phytostenol ester, and (ii) a *conjugated* fatty acid or *conjugated* fatty acid ester having from 6 to 24 carbon atoms, nor a method of reducing serum cholesterol content via the administration of such a preparation.

❸ Even if it were assumed for argument's sake that a *prima facie* case of obviousness had been established based upon the cited references, which it has not, Applicant's showing of significantly improved results overcomes such a *prima face* case.

❹ The Examiner has completely misinterpreted the evidence of significantly improved results provided by Applicant.

Before addressing the Examiner's rejection and the four points set out above, Applicant would like to reiterate that the claimed invention is directed to hypocholesteremic preparations comprising at least one component (a) selected from the group consisting of phytostenols and phytostenol esters *and* at least one component (b) selected from *conjugated* fatty acids having from about 6 to about 24 carbon atoms and glycerides of *conjugated* fatty acids having from about 6 to about 24 carbon atoms; and to methods of reducing serum cholesterol content in a mammal comprising administering such a preparation to a mammal in an amount effective to reduce serum cholesterol content in the mammal.

A Mention of "Unsaturated Fatty Acids" does not Equate to a Suggestion to Use Conjugated Fatty Acids, & Thus the Cited References Fail to Teach or Suggest Conjugated Fatty Acids

To be clear, it is well-known that the term "conjugated", when referring to chemical bonds, means two or more double bonds with alternating single bonds, for example, -CH=CH-CH=CH-CH=CH-. Conjugation is a subset of polyunsaturation. All conjugated compounds are polyunsaturated, but NOT all polyunsaturated compounds are conjugated. To the contrary, most polyunsaturated compounds are not conjugated. Moreover, most polyunsaturated compounds in nature are not conjugated. For example, linoleic acid which occurs frequently in nature is well known to be 9,12-octadecadienoic acid, the "9,12" designation indicating the position of the two double bonds in the 18 carbon acid. To obtain conjugated linoleic acid, one needs to employ chemical and/or bacterial processes to isomerize the acid. While conjugated linoleic acid does occur naturally in the meat and milk of cows, it does not occur naturally in vegetable oils, such as rapeseed oil.

Jandacek:

The Examiner continues to argue that "Jandacek teaches broadly the usefulness of phytosterols such a β-sitostenol along with saturated and unsaturated fatty acids having form 6 to 18 carbon atoms including any conjugated fatty acids having from 6 to 18 carbon atoms, e.g., conjugated linoleic acid, in the instant claimed method." (*See*, Paper No. 16, p. 3 (*emphasis in original*)). THE EXAMINER'S STATEMENT IS INCORRECT. JANDACEK DOES NOT

TEACH OR SUGGEST THE USE OF CONJUGATED FATTY ACIDS IN CONJUNCTION WITH PHYTOSTENOLS TO LOWER SERUM CHOLESTEROL. JANDACEK DOES NOT MENTION CONJUGATION.

Jandacek discloses the use of a steroid solubilizing agent in conjunction with phytosterols for the reduction of cholesterol levels. (*See*, Jandacek, col. 2, lines 1-5). Jandacek is directed to increasing the solubility of phytosterols in edible oils. In an effort to increase the solubility of a phytosterol in an edible oil, Jandacek teaches the use of a steroid solubilizing agent which may be selected from "free fatty acids, fatty acids esters and alkanols." (*See*, Jandacek, abstract). Jandacek does not teach the use of fatty acids *per se* to lower cholesterol levels. In fact, Jandacek does NOT associate any hypocholesterolemic effect with the fatty acids taught therein. Moreover, Jandacek does not teach the use of any polyunsaturated acids, let alone conjugated acids. There is no teaching or suggestion in Jandacek that the solubility of a phytosterol in an edible oil could be increased by the incorporation of a *conjugated* fatty acid, and thus there is no motivation to modify its teachings in such a way.

Miettinen:

The Examiner also insists that Miettinen "teaches broadly the usefulness of fatty acids esters of β-sitosterol (β-sitostenol) and β-sitostanol containing approx. 2-22 carbon atoms and up to about 3 double bonds in the instant claimed method . . .." (*See*, Paper No. 16, p. 3 (*emphasis in original*)). The Examiner contends that Miettinen discloses the use of fatty acid ester mixtures based upon rapeseed oil, and that "it is well known that rapeseed oil contains about 90% unsaturated fatty acids having one or more double bonds." (*See, id.*). AGAIN, THE EXAMINER'S STATEMENTS ARE UNTRUE. MIETTINEN DOES NOT TEACH OR SUGGEST THE USE OF FATTY ACIDS HAVING 'UP TO ABOUT THREE DOUBLE BONDS' IN A MIXTURE WITH A PHYTOSTENOL COMPOUND.

The precise language of the portion of Miettinen cited by the Examiner in Paper No. 12, in support of the proposition that the reference teaches esters of fatty acids containing approx. 2-22 carbon atoms and up to about 3 double bonds, namely page 3, lines 42-45, reads in pertinent part as follows:

> . . . [a phytostanol] is esterified with different fatty acid ester mixtures by a commonly known chemical interesterification technique. A methyl ester mixture of the fatty acids of any vegetable oil can be used in the reaction. One example is a rapeseed oil based methyl ester, but any fatty acids which contain approx. 2-22 carbon atoms are usable.
>
> (Miettinen, page 3, lines 42-45 (*citations omitted*)).

Miettinen contains no teaching or suggestion to use conjugated acids to esterify phytostenols, let alone to use conjugated acids in a mixture with phytostenol compounds. Miettinen does not even specifically recite the usage of polyunsaturated acids. The Examiner has extrapolated the mention of rapeseed oil, which does in fact contain some amounts of NON-CONJUGATED, polyunsaturated acids, into an alleged teaching of conjugated fatty acids. Most rapeseed oils contain some small amount of linolenic acid which has three NON-CONJUGATED double bonds. However, teaching esterification with fatty acid ester mixtures based upon vegetable oils, including an oil which may contain some acids having three double bonds, is not equivalent to a teaching to use specific fatty acids having certain numbers of double bonds, or specific fatty acids having conjugated double bonds. Moreover, Miettinen is directed to phytosterol ESTERS, not a mixture of a phytosterol and a conjugated fatty acid.

While the Examiner is correct that it is known that rapeseed oil contains about 90% unsaturated fatty acids, it should also be noted that rapeseed oils (and most vegetable oils in general) are NOT known to contain CONJUGATED fatty acids. As can be seen in a comparison of most common rapeseed oils from various origins, the only polyunsaturated acids present in the oil are NON-CONJUGATED (*i.e.*, linoleic, docosadienoic and linolenic). (*See, e.g.*, Swern, Daniel, (Ed.), Bailey's Industrial Oil and Fat Products, 4th ed., Vol. 1, pp. 416, (1979), (a copy of which is attached for the Examiner's convenience). It is also known that the only common vegetable sources of conjugated acid oils are tung oil and oiticica oil. (*Id.* at p. 286).

Hasegawa:

The Examiner argues that Hasegawa provides "further motivation for the instant method." (*See*, Paper No. 16, p.3). The Examiner contends that Hasegawa teaches linoleic acid as being useful for lowering serum cholesterol.

Hasegawa contains no teaching or suggestion that would motivate one of ordinary skill in the art to modify its teachings to include a conjugated fatty acid along with a phytostenol compound. Given the lack of any teaching or suggestion of conjugated fatty acids, Applicant is unsure how the reference provides "further motivation for the instant method."

Lack of Prima Facie Obviousness:

The Examiner acknowledges that neither Jandacek, nor Hasegawa, teaches the use of phytosterols and *conjugated* fatty acids for lowering serum cholesterol levels. (*See*, Paper No. 12, page 4). However, the Examiner maintains that the cited references suggest the use of a conjugated fatty acid. Applicant respectfully disagrees. None of the four references teaches conjugated fatty acids. None of the four references teaches a component which contains conjugated fatty acids. There is no suggestion to use conjugated fatty acids in a mixture with a phytostenol compound.

Even if the Examiner were to maintain that the broad recitation of "fatty acids", including unsaturated fatty acids, somehow includes a teaching or suggestion of conjugated fatty acids, the cited references would still fail to satisfy the necessary criteria for *prima facie* obviousness as none of the four references contains a teaching or suggestions which would motivate one of ordinary skill in the art to modify the teachings of the references to use a conjugated fatty acid.

IT IS EXTREMELY WELL-SETTLED THAT THE FACT THAT A REFERENCE CAN BE MODIFIED IS INSUFFICIENT WITHOUT A TEACHING OR SUGGESTION IN THE PRIOR ART AS TO THE DESIRABILITY OF THE MODIFICATION. (*See*, M.P.E.P. §2143).

Finally, one of ordinary skill in the art would NOT have a reasonable expectation of success *based upon the cited references*. The Examiner has argued that one of ordinary skill in the art would find a reasonable expectation of success because it would have been "reasonably expected that combining a phytosterol and . . . a conjugated fatty acid . . . known useful for the same purpose . . . would improve the therapeutic effect . . .." (*See*, Paper No. 16, page 3). THE PRIOR ART DOES NOT TEACH THE TWO CLAIMED COMPONENTS AS BEING

USEFUL FOR THE SAME PURPOSE. THE EXAMINER HAS ARGUED THAT THE PRIOR ART SUGGESTS ONE OF THE COMPONENTS. HOWEVER, THE PRIOR ART DOES NOT TEACH CONJUGATED FATTY ACIDS, AND NO MOTIVATION TO MODIFY THE TEACHINGS TO USE CONJUGATED FATTY ACIDS IS PRESENT IN THE CITED REFERENCES. THUS, THE CLAIMED INVENTION IS NOT SIMPLY THE COMBINATION OF TWO COMPONENTS KNOWN FOR THE SAME PURPOSE.

Accordingly, Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness, as none of the three criteria necessary to establish a *prima facie* case of obviousness has been satisfied. Thus, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §103(a).

Indicia of Non-Obviousness:

Lastly, even if it were assumed, for argument's sake, that a *prima facie* case of obviousness could be established based upon the cited references, which it cannot, any such alleged *prima facie* case of obviousness would be overcome by Applicant's showing of synergism between the phytostenol(ester)s and the conjugated fatty acids and the unexpected, significantly improved results of the claimed preparations compared to the prior art.

MOREOVER, APPLICANT SUBMITS THAT THE EXAMINER HAS MISINTERPRETED THE EVIDENCE SET FORTH IN THE SPECIFICATION AND THAT SAID EVIDENCE ADEQUATELY REBUTS ANY ALLEGED *PRIMA FACIE* CASE OF OBVIOUSNESS.

The Examiner has argued "that lauric acid in lauric acid β-sitostanol ester or lauric acid β-sitostenol ester employed in the testing herein is not even an unsaturated carboxylic acid, which is not a conjugated fatty acid [and t]hus, these two compounds are not within the scope of the claimed invention" (See, Paper No. 16, page 4). Based upon this argument, the Examiner contends that the results shown for the combination of a lauric acid ester of β-sitostenol or β-sitostanol and conjugated linoleic acid "[are] not deemed relevant." (*See, id.* at 4-5).

APPLICANT'S CLAIMED INVENTION IS DIRECTED TO hypocholesteremic preparations comprising: at least one component (a) selected from the group consisting of phytostenols **and** phytostenol esters; ***and*** **at least one component (b)** selected from *conjugated* fatty acids having from about 6 to about 24 carbon atoms and glycerides of *conjugated* fatty acids having from about 6 to about 24 carbon atoms; and to methods of reducing serum cholesterol content via administration of such preparations.

APPLICANT WOULD LIKE TO BRING TO THE EXAMINER'S ATTENTION THE FACT THAT THE LAURIC ACID SITOSTENOL **ESTERS** LISTED IN TABLE 1 ARE **PHYTOSTENOL ESTERS** AND THEIR COMBINATION AS A MIXTURE WITH CONJUGATED LINOLEIC ACID IS MOST CERTAINLY WITHIN THE SCOPE OF THE PRESENT INVENTION.

Applicant respectfully submits that the combination of phytostenol(ester)s and conjugated fatty acids in accordance with Applicant's invention perform better than either component alone in reducing serum cholesterol levels. This is clearly evidenced by the Examples set forth in Applicant's Specification, beginning at page 8, line 17. As can be seen from Table 1, at page 9, the combinations decrease the serum cholesterol levels in amounts greater than either component alone. The Examiner has argued that the data shows less than additive therapeutic effects. APPLICANT RESPECTFULLY SUBMITS THAT THE EXAMINER IS INCORRECT. Example C5 shows the effect of 10% by weight of conjugated linoleic acid alone. After 48 hours, the "% rel." of radio-labeled cholesterol is 60% (a greater decrease from 100% is BETTER). Example C1 shows the effect of 10% by weight of β-sitostenol alone. After 48 hours, the "% rel." of radio-labeled cholesterol is 35%. HOWEVER, as shown in Example 1, half the amount of β-sitostenol (5% by weight) and half the amount of conjugated linoleic acid (5% by weight), in combination, result in a "% rel." of radio-labeled cholesterol of 23%. The Examiner is incorrect to argue that because Example C5 results in a 40% decrease, and Example C1 results in a 65% decrease, that the 77% decrease of Example 1 is less than additive. Such logic would require a relative reduction of greater than 105%. Additionally, as is the case with most "purifications" or "removals", the removal of each additional amount of an undesired impurity (*i.e.*, cholesterol) is progressively more difficult.

Applicant submits that a 77% relative reduction using half the amounts of a phytostenol and a conjugated fatty acid, compared to a 40% relative reduction and a 65% relative reduction using twice the amount of either material alone, is evidence of both a synergistic effect associated with the combination and a significant improvement over prior art hypocholesteremic preparations.

It is submitted that Applicant's showing sufficiently rebuts any alleged *prima facie* case of obviousness. Therefore, withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

In view of the remarks set forth above, Applicant submit that all pending claims patentably distinguish over the prior art of record and known to Applicant, either alone or in combination. Accordingly, reconsideration, withdrawal of the rejections and a Notice of Allowance are respectfully requested.

Respectfully submitted,

BERND FABRY

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Appendix A: Swern, Daniel, (Ed.), Bailey's Industrial Oil and Fat Products, 4th ed., Vol. 1, pp. 416, (1979) (4 pages)